

## REMARKS

Claims 45, 46, 58, 59, 73, and 75-77 are pending in this application. Claims 45, 46, 58, 59, 73, and 75-77 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter “Relyveld”) in combination with Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter “Gerhart”) and Constantz et al. (U.S. Patent No. 5,782,971; hereinafter “Constantz”). Claims 45, 46, 58, 59, 73, and 75-77 are also rejected for obviousness-type double patenting over claims 56 and 57 of U.S. Patent No. 6,541,037. By this reply, Applicants amend claim 45, add new claim 78, and address each of the Examiner’s rejections.

### Support for the Amendment

Support for the amendment to claims 45 is found in the present specification at, e.g., page 29, lines 11-13, and page 29, line 25, through page 30, line 1, and in the priority document, U.S. Patent No. 6,541,037, at, e.g., col. 6, lines 25-27, and col. 7, lines 22-26. Support for new claim 78 is found in the specification at, e.g., page 29, lines 21-23, and in U.S. Patent No. 6,541,037 at, e.g., col. 7, lines 11-21. No new matter is added by the amendment.

### Obviousness-type Double Patenting Rejection

Claims 45, 46, 58, 59, 73, and 75-77 are rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 56 and 57 of U.S. Patent No. 6,541,037. In response to this rejection, Applicants submit a terminal disclaimer herewith, waiving the terminal portion of the term of the entire patent to be granted upon the above-identified application subsequent to the expiration date of U.S. Patent No. 6,541,037. In light of

the terminal disclaimer, Applicants respectfully request that the rejection of claims 45, 46, 58, 59, 73, and 75-77 for obviousness-type double patenting be withdrawn.

Rejections under 35 U.S.C. § 103

*Relyveld, Gerhart, and Constantz*

Claims 45, 46, 58, 59, 73, and 75-77 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart, and Constantz. The Office states “that there is no support for the limitation “said calcium phosphate comprises greater than or equal to 40 wt% of said composition’ in Applic. No. 08/729,342 (October 16, 1996). The priority of October 16, 1996 is not granted” (Office Action, p. 6).

During a telephonic interview with Examiner Soroush on October 5, 2009 (the “Interview”), Applicants’ representative discussed removing the phrase “wherein said calcium phosphate comprises greater than or equal to 40 wt% of said composition” from independent claim 45 in order to perfect entitlement to the October 16, 1996, filing date of U.S. Patent No. 6,541,037. Examiner Soroush agreed that this amendment would entitle the present application to a priority date of October 16, 1996, and that this would remove Constantz as prior art against present claims 45, 46, 58, 59, 73, and 75-77. Applicants have so amended independent claim 45, and thus Constantz, which has a later filing date of March 19, 1997, should be removed as prior art to the present application.<sup>1</sup>

During the Interview, Examiner Soroush stated that, even in the absence of Constantz, the combination of Relyveld and Gerhart would render claims 45, 46, 58, 59, 73, and 75-77 obvious.

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<sup>1</sup>Applicants have also amended claim 45 to recite that the composition forms a poorly crystalline apatitic calcium

Applicants' representative disagreed, explaining that the combination of Relyveld and Gerhart fails to teach or suggest all of the limitations of present independent claim 45, and claims dependent therefrom. In particular, Relyveld and Gerhart fail to teach or suggest a calcium phosphate composition that hardens in an endothermic reaction and that forms a poorly crystalline apatitic (PCA) calcium phosphate, which are recited as characteristics of the composition of present claims 45, 46, 58, 59, 73, and 75-77. Instead, Gerhart describes a bone cement that is cured in an exothermic reaction, stating:

The present invention is directed to a biodegradable cement composition adapted for use in the surgical repair of living bone and for the controlled-release delivery of pharmaceutical agents. The composition comprises a particulate biocompatible calcium phosphate ceramic and a resorbable calcium salt dispersed in a cross-linked biodegradable polyester matrix.

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*The cross-linking reaction employed to "cure" the present composites is only mildly exothermic compared to, for example, PMMA polymerization.*

(Gerhart, col. 4, lines 19-25, and col. 8, lines 30-32; emphasis added.)

Examiner Soroush stated that, absent evidence to the contrary, the endothermic hardening of the composition of present claims 45, 46, 58, 59, 73, and 75-77 was not sufficiently different from the mildly exothermic hardening of Gerhart's calcium phosphate cement, and thus the endothermic hardening limitation did not overcome the present obviousness rejection over the combination of Gerhart and Relyveld. Examiner Soroush stated that she would consider "data with regards to the endothermic property claimed vs. the property described in the prior art" showing that the composition of present claims 45, 46, 58, 59, 73, and 75-77 exhibits unexpected

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phosphate at body temperature. This new limitation is fully supported by the priority document, U.S. Patent No. 6,541,037.

properties not present in the prior art (Interview Summary dated October 16, 2009).

In response, Applicants submit the Declaration of Dr. Aliassghar N. Tofighi (the “Tofighi Declaration”), which states that the composition of present independent claim 45, and claims dependent therefrom, exhibits at least two properties that are absent from the composition of Gerhart. First, the composition of present independent claim 45, and claims dependent therefrom, form a PCA calcium phosphate upon hardening; the Gerhart composition does not (see ¶¶ 3, 4, and 6 of the Tofighi Declaration). Second, the composition of present independent claim 45, and claims dependent therefrom, hardens in an endothermic reaction as a result of the interaction of calcium phosphates (e.g., amorphous calcium phosphate or poorly crystalline calcium phosphate), whereas the Gerhart composition cures in a mildly exothermic reaction as a result of the polymerization of biodegradable polyester with a chemical cross-linking agent in a different, curing reaction (see ¶¶ 3, 5, and 7 of the Tofighi Declaration).

Unlike the composition of present claims 45, 46, 58, 59, 73, and 75-77, the Gerhart composition would not form a PCA calcium phosphate (see ¶¶ 3 and 6 of the Tofighi Declaration). The composition of present claims 45, 46, 58, 59, 73, and 75-77 forms a PCA calcium phosphate due to rapid crystallization of a metastable phase, which also involves the release of carbonate ions, a fraction of which is incorporated into the apatite lattice and gives rise to a nonstoichiometric poorly crystalline apatite rich in  $\text{HPO}_4^{2-}$  (see ¶ 4 of the Tofighi Declaration). This reaction is absent from the curing reaction that occurs during the formation of the Gerhart composition (see ¶ 6 of the Tofighi Declaration). The Gerhart composition, which is a “polymer matrix [that] serves as a supporting binder for particles of biocompatible inorganic salts and ceramics” (col. 2, lines 34-36), cures via the polymerization of a biodegradable

polyester with a chemical cross-linking agent to form a solidified cement matrix (see col. 5, lines 25-27). As stated in the Tofighi Declaration, it is the polymerization of the polyester in the curing reaction that produces the solidified cement; curing of the Gerhart composition does not involve a reaction of the calcium salts and ceramics (see ¶ 6). Furthermore, the calcium salts and ceramics do not appear to contribute to a conversion of the Gerhart composition into a PCA calcium phosphate, as occurs in the composition of present claims 45, 46, 58, 59, 73, and 75-77. Instead, according to Gerhart's description of the process, the calcium salts and the ceramic component (termed the "particulate phase") "act[] as a strength-imparting filler, much like the aggregate component of concrete" (Gerhart, col. 6, lines 40-45). Gerhart states:

Initially, particulate calcium salts in the cement are eluted from the polyester matrix by body fluids creating small voids or cavities in the polymer matrix. Over time, the more slowly resorbable particulate ceramic component is wholly or partially resorbed, and the polyester matrix itself degrades in vivo into its component non-toxic assimilable dicarboxylic acids, and dihydric or polyhydric alcohols.

(Gerhart, col. 2, lines 49-56.) Thus, the calcium salts promote the formation of "small voids or cavities in the polymer matrix" that may "be filled in by new bone" (Gerhart, col. 2, lines 49-58), while the ceramic component, which is "wholly or partially resorbed over time," is provided to promote bone growth via osteoconduction (Gerhart, col. 2, lines 49-56, and col. 6, lines 53-58). Thus, in contrast to the composition of present claims 45, 46, 58, 59, 73, and 75-77, the Gerhart composition does not harden as a result of the reaction of a calcium phosphate and does not convert upon hardening into a PCA calcium phosphate.

In addition, the Gerhart composition hardens in a mildly exothermic reaction rather than an endothermic reaction. The Gerhart composition hardens due to the polymerization of a polyester with a chemical cross-linking agent in a curing reaction. Gerhart states:

The preparation of the present composite cement typically involves combining the polyester and the cross-linking agent into a substantially homogeneous mixture, and adding the particulate calcium phosphate ceramic and calcium salt to form a moldable composite cement mass which hardens on curing, *i.e.*, *completion of the cross-linking reaction.*

(Gerhart, col. 5, lines 37-43; emphasis added.) It is this cross-linking reaction that generates heat in a mildly exothermic reaction (Gerhart, col. 8, lines 30-32). As discussed above, according to Gerhart's description of the process, the calcium salts and ceramics in the Gerhart composition do not contribute to this curing reaction.

In contrast, the composition of present claims 45, 46, 58, 59, 73, and 75-78 hardens in an endothermic reaction as a result of the fast hydrolysis of the amorphous phase of the composition into poorly crystalline apatite (see ¶ 5 of the Tofighi Declaration). The setting reaction uses heat (e.g., body heat) to begin and develop. This is not true of the Gerhart composition and is an unexpected property of the calcium phosphate composition of present claims 45, 46, 58, 59, 73, and 75-77. Moreover, the endothermic nature of the reaction that produces the composition of present claims 45, 46, 58, 59, 73, and 75-77 allows the reaction progress to be controlled by regulating the amount of heat available to support the reaction (see ¶ 5 of the Tofighi Declaration). Thus, the composition components react minimally at room temperature and below, but harden in about 30 minutes once exposed to body temperature. The Gerhart composition fails to exhibit this characteristic.

In view of the differences discussed above between the composition of present claims 45, 46, 58, 59, 73, and 75-78 and the Gerhart composition, Gerhart fails to teach or suggest a composition having each and every limitation of the composition of present claims 45, 46, 58, 59, 73, and 75-78.

Relyveld fails to cure the deficiencies of Gerhart. Relyveld discloses a calcium phosphate gel that should be administered as a fine, particulate *suspension* (see, e.g., col. 2, lines 2-9). Relyveld fails to teach or suggest a delivery composition formulated as an injectable paste that hardens in an endothermic reaction to form a poorly crystalline apatitic calcium phosphate. Thus, Relyveld, whether considered singly or in combination with Gerhart, fails to teach or suggest a composition having each and every limitation of present claims 45, 46, 58, 59, 73, and 75-78.

The rejection of claims 45, 46, 58, 59, 73, and 75-77 under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart, and Constantz should be withdrawn and should not be applied to present claims 45, 46, 58, 59, 73, and 75-78.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the pending claims are in condition for allowance, and a notice to that effect is respectfully requested.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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For

  
Paul T. Clark  
Reg. No. 30,162

Todd Armstrong, Ph.D.  
Reg. No. 54,590

Clark & Elbing LLP  
101 Federal Street  
Boston, MA 02110  
Telephone: 617-428-0200  
Facsimile: 617-428-7045